REMARKS

The present amendment cancels several claims and places the application in condition for allowance or in better form for consideration on appeal. Therefore, in accordance with MPEP §714.12, Applicants respectfully request that the present amendment and remarks be entered.

Claims 1-104, 107, 108, 132, 143, 165-166 and 172-183 are canceled. Claims 105, 106, 109-131, 133-142, 144-164, 167-171, 184 and 185 are pending and under examination.

Claims 144 and 147 have been amended to depend from a non-canceled base claim. Claim 184 has been amended merely to insert the art-recognized abbreviation "CHO". No new matter is added.

Specification

As requested by the Examiner, the specification has been amended to capitalize trademark names and to further describe Gene-Activated® GCB by reference to U.S. 5,641,670. Applicants note that gene activation technology was described, and U.S. 5,641,670 was cited and incorporated by reference, in the application as filed, e.g., at page 30, lines 5-8. No new matter is added.

Claim Objections

The claim objections have been addressed by canceling claim 166 and amending claim 184 to add the abbreviation "(CHO)" for "Chinese hamster ovary".

Rejections Under 35 U.S.C. §112, 2d Paragraph

Claims 144-147 are rejected as depending from canceled claims. These claims have been amended to depend from pending claim 139, thereby obviating the rejection.

Rejections Under 35 U.S.C. §103

Claims 105, 106, 109-171, 184 and 185 remain rejected as unpatentable over Friedman in view of Smith. Claims 132, 143 and 165 were canceled in the last reply and claim 166 is canceled by the present amendment for other reasons. The rejection is respectfully traversed.

Smith has nothing to do with GCB. There is no suggestion or motivation in Smith to harvest any protein, much less a specific protein such as GCB, from the HT29 cells. The Examiner argues that motivation to harvest GCB expressed by the HT-29 cells of Smith is provided by Friedman's teaching of the importance of carbohydrate remodeling in GCB function. The Examiner concludes: "Therefore, there is motivation to obtain a hmGCB by known means. *Kifunensine is one of such well known means used in remodeling.*" As the Examiner acknowledges, kifunensine is merely one of many methods used in carbohydrate remodeling. However, the fact that it may be desirable or important to produce high mannose GCB does not make any one particular method of doing so obvious, particularly when many other alternatives exist. Indeed, Friedman (which relates specifically to GCB) lists several types of methods for carbohydrate remodeling, including using mutant cell lines deficient in certain carbohydrate synthetic pathways and chemical modification of the oligosaccharide of the purified recombinant GCB. Friedman does not suggest using any mannosidase inhibitor. Thus, the Examiner has not addressed the substance of Applicants' argument that, without using the claims as a template, it would have been impossible to choose kifunensine from the large group of known carbohydrate modifiers, to combine with Friedman. Applicants maintain that the Examiner has used hindsight to pick and choose the elements of the claims from the art. This is impermissible. Accordingly, a prima face case of obviousness has not been made.

In response to Applicants' arguments regarding surprising results, discussed in the Reply filed July 14, 2003, the Examiner argues that Applicants' showing of an approximately 4-fold increase in GCB uptake was not unexpected in view of Furbish et al. (BBA, 1981, 673:425-434), which discloses that isolated GCB treated with various glycosidases showed a 5-fold increase in uptake. Applicants strongly disagree that Furbish et al. provides the proper basis for comparison

for Applicants' results. Treating an isolated glycoprotein directly with a glycosidase to remodel the oligosaccharide structure of the glycoprotein (as taught by Furbish) is a completely different type of carbohydrate remodeling method than treating a cell with a glycosidase inhibitor (in this case, a mannosidase inhibitor), as claimed. The Furbish method directly exposes an isolated glycoprotein to an oligosaccharide-remodeling enzyme and can thus be expected to be very efficient. Because a mannosidase inhibitor acts to inhibit an enzyme in the N-terminal glycosylation pathway during glycoprotein synthesis in the cell, it affects the oligosaccharide composition of glycoproteins indirectly. Thus, even if a skilled artisan had been motivated to try the claimed methods (which of course is not sufficient for a prima case of obviousness), the claimed method would have been expected to be inefficient compared to the direct, glycosidase remodeling method of Furbish. As such, the fact that the claimed method results in approximately the same level of increase in uptake as Furbish is, by itself, surprising.

Indeed, Smith suggests that at most, one could expect a 50-75% change in a functional aspect of a glycoprotein expressed from a kifunensine treated cell. That is, Smith teaches that "the receptor molecule on the bacteria recognizes high-mannose oligosaccharides on the HT-29 cell surface" (Smith 7:27-30). However, treating a cell with either kifunensine or deoxymannojirimycin increased the number of radioactive bacteria bound to HT-29 cells by only 50-75 % (Smith 8:32-35). Therefore, in view of Smith, Applicants' results showing that GCB harvested from kifunensine treated cells showed a 400 % increase in function (e.g., uptake) is indeed unexpected. Accordingly, even if a prima facie case of obviousness had been made (which Applicants do not concede), Applicants' unexpected results are sufficient to overcome it.

In light of the foregoing, Applicants respectfully request withdrawal of the rejection.

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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